PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Association Between Disease-modifying Therapies for Multiple Sclerosis and Healthcare Utilization on a Population Level: A Retrospective Cohort Study
AUTHORS	Al-Sakran, Lina; Marrie, Ruth Ann; Blackburn, David; Knox, Katherine; Evans, Charity

VERSION 1 – REVIEW

REVIEWER	Dr. Raffaele Palladino Department of Public Health, University Hospital "Federico II" of Naples, Italy
REVIEW RETURNED	11-Sep-2019

GENERAL COMMENTS	With the present study Al-Sakran and colleagues aimed to assess the association between DMTs and healthcare utilisation constructing a population-based study using data from from Saskatchewan, Canada from 1997–2016. The study is interesting and employs appropriate statistical methodology to answer the proposed research questions. Please find below comments authors might wish to consider that might further improve the manuscript. - The authors describe the use two cohorts to conduct the study, the general population cohort and the MS cohort. Whilst it is clear the scope of this by reading statistical analysis section and results, at first it might read rather confusing (especially in the abstract). I would suggest to explain better in the abstract the reason for that and also include a study design sub-section at the beginning of the method section. - To model trends authors employed a linear regression model, which is very common in econometrics but less common in biostatistics, where a Poisson regression model is preferred. Please justify. - I would also like to ask authors reasons why they model healthcare utilisation at population level rather then using individual-level data setting population as offset. By modelling individual-level data authors could have controlled for confounders and improved precision and power. This might have allowed to estimate confounders-adjusted rates and not only age and sex stratified rates. Please justify. - Finally, it is not entirely clear whether in their models authors accounted for the change in the number and types of DMTs available over time.

	- A very minor point is about the data presentation. Overall graphs are clear but I would suggest to replace the current label of the x-scale opting for a 5-year study period. The axis might look much less busier and easier to read

REVIEWER	Kate Wang Monash University, Australia
REVIEW RETURNED	14-Sep-2019

GENERAL COMMENTS	The study is overall well written, using a very large pool of administrative data representative of the population. The authors did a great job describing their findings and discussing their results. However, I do propose the following suggestions for improvement: Please clearly state the study design 'retrospective cohort study' in the abstract. Authors should consider including a table which describes the basic baseline characteristics of the population. Perhaps this may be done individually in two separate columns comparing the two different cohorts. While the authors explained why individual covariates were not included, I feel it is important that some covariates (such as the use of other MS medications) is important as the result could be easily confounded by the use of other MS medications. The point 'Observational studies cannot adjust or assess all potential (unknown) confounders.' was not really discussed in the manuscript. Authors should consider including in their introduction the current guidelines on prescribing DMTs in Canada. For eg, is this 1st or 2nd line treatment? How often is this used in comparison to other treatment options? Is this used together with other treatments? What happens if people died or lost to follow up during the study? How are these people considered? In Figure 2, it was interesting that the mean length of hospital stay in the MS cohort went up and down over the rather (rather than consistently up or down). Does the authors have a possible explanation for this? Is it possible to separate the years on the x-axis for figures 2 and 3? It is a bit difficult to read at the moment. Perhaps put the years on an angle like it was done in figure 1?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Dr. Raffaele Palladino
Institution and Country: Department of Public Health, University Hospital "Federico II" of Naples, Italy
Please state any competing interests or state ‘None declared’: No competing interests

Please leave your comments for the authors below:

With the present study Al-Sakran and colleagues aimed to assess the association between DMTs and healthcare utilisation constructing a population-based study using data from Saskatchewan, Canada from 1997–2016. The study is interesting and employs appropriate statistical methodology to answer the proposed research questions. Please find below comments authors might wish to consider that might further improve the manuscript.

We thank Dr Palladino for the supportive and helpful comments, and have addressed them individually below.

- The authors describe the use two cohorts to conduct the study, the general population cohort and the MS cohort. Whilst it is clear the scope of this by reading statistical analysis section and results, at first it might read rather confusing (especially in the abstract). I would suggest to explain better in the abstract the reason for that and also include a study design sub-section at the beginning of the method section.

We have revised the abstract to better explain the reason for the two cohorts. It now reads: "*We used population-based health administrative data from Saskatchewan, Canada from 1997–2016. To test for associations at the population level, we identified two cohorts. The general population cohort included all Saskatchewan residents ≥18 years who were drug plan beneficiaries. The MS cohort included individuals ≥18 years, identified using a validated definition (≥3 hospital, physician or drug claims for MS).*"

We have also added a Study Design sub-section to the Methods to help clarify the reason for the two cohorts as suggested. This section reads: "*This retrospective cohort study examined exposure (DMTs) and outcomes (healthcare utilization) on a population level, rather than individual level. To do this, we created two separate cohorts. The general population cohort included all Saskatchewan residents who were beneficiaries of the provincial drug plan and were ≥18 years old. The MS cohort included drug plan beneficiaries ≥18 years old who were identified to have MS between January 1, 1996 and December 31, 2016, based on a previously validated algorithm requiring ≥3 hospital (ICD-9: 340, ICD-10-CA: G35), physician (ICD-9: 340) or drug claims (Appendix A) for MS.*"

- To model trends authors employed a linear regression model, which is very common in econometrics but less common in biostatistics, where a Poisson regression model is preferred. Please justify.

Thank you for the comment. We have re-run the trend analyses using Poisson regression as suggested, and have made the required changes in the manuscript (Methods and Results) and Figures to demonstrate this.

- I would also like to ask authors reasons why they model healthcare utilisation at population level rather then using individual-level data setting population as offset. By modelling individual-level data authors could have controlled for confounders and improved precision and power. This might have allowed to estimate confounders-adjusted rates and not only age and sex stratified rates. Please justify.

The decision to model healthcare utilization and DMT use at the population-level rather than individual level was made for two reasons. First, it allowed us to examine associations in a novel way. Second, it also allowed us to examine the impact of DMT use on the healthcare system which is particularly valuable from a policy perspective, rather than just on the individual subjects. Previous studies have examined DMTs and healthcare utilization and costs on individual levels, albeit with conflicting results. We felt that that a population-level approach would add to the existing literature, as well as provide a different perspective (i.e. payer/policy maker). We have a section in our Discussion that attempts to address this, as well as provide a reference to a paper that uses a similar methodology: *"This study is novel in that it examined the association of DMTs and healthcare utilization in an MS cohort on a*

population, rather than individual, level. This allowed us to examine the impact of DMT use on the healthcare system, and from a policy perspective which must balance the cost of DMTs with potential improvement in health at the health system level.. This ecological approach is similar to other studies that have looked at population-level drug utilization, interventions, and outcomes in other diseases such as heart failure and diabetes.[40] Outcomes related to healthcare utilization, and in particular hospitalizations, are of interest to payers and policy makers; hospitalizations are the largest component of healthcare resource use, and can also be surrogate measures for disease worsening.[13 41]"

- Finally, it is not entirely clear whether in their models authors accounted for the change in the number and types of DMTs available over time.

We did not specifically account for the change in number or types of DMTs available over time, as distinctions between the different DMTs were not made in our analyses (i.e. they were considered as a class effect). We have added a sentence to clarify this in the Methods. The section now reads: *"Utilization of DMTs (Appendix A) was measured for each year between 1997 and 2016 and reported as the total number of dispensations for any DMT, and the total number of individuals receiving at least one DMT dispensation. DMT use was measured on a class level, rather than reported for individual agents. Although the first DMT (interferon-beta-1b) was approved for use in Canada in 1996, it was not available through the Saskatchewan drug plan until December 1997 (Appendix A). During the study period, the majority of DMTs prescribed were first-line agents, which include interferon-beta-1a/1b, glatiramer acetate, dimethyl fumarate, and teriflunomide (Appendix A). In Saskatchewan, prescriptions are primarily dispensed in one-month quantities, including the DMTs that were available during the study period."*

We also discuss the class effect consideration in our limitations section. It reads*: "…As is common with administrative data, we did not have access to important clinical factors that may affect hospitalization rates such as type of MS[13] and disease severity.[39] However, because we were evaluating healthcare utilization at the population level, this individual-level data was not necessary. Finally, we considered a class effect of the DMTs and therefore were not able to differentiate outcomes related to specific DMTs."*

- A very minor point is about the data presentation. Overall graphs are clear but I would suggest to replace the current label of the x-scale opting for a 5-year study period. The axis might look much less busier and easier to read

Thank you for the suggestion – we have revised the scaling on the x-axis for all three figures.

Reviewer: 2

Reviewer Name: Kate Wang
Institution and Country: Monash University, Australia Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below:

The study is overall well written, using a very large pool of administrative data representative of the population. The authors did a great job describing their findings and discussing their results. However, I do propose the following suggestions for improvement:

We thank Dr Wang for her supportive and helpful comments, and have addressed them individually below.

Please clearly state the study design 'retrospective cohort study' in the abstract.

We have added the study design to the first sentence of the Methods section of the Abstract as suggested: It now reads: *"This retrospective cohort study used population-based health administrative data from Saskatchewan, Canada from 1997–2016."*

Authors should consider including a table which describes the basic baseline characteristics of the population. Perhaps this may be done individually in two separate columns comparing the two different cohorts.

Unfortunately, because this was a population-level study by design, we do not have the individual baseline characteristics available for the MS cohort or the general population cohort. We did, however, describe the population of Saskatchewan and discuss the incidence and prevalence of MS in Saskatchewan to provide the readers some context.

While the authors explained why individual covariates were not included, I feel it is important that some covariates (such as the use of other MS medications) is important as the result could be easily confounded by the use of other MS medications.

We agree that covariates such as concurrent medication use could affect study results. However, as this was a population-level study, we did not have individual level covariates available to include in the analyses. We do address this limitation in our Discussion, but have specifically added concurrent medications to the comment. The section now reads: *"It was not possible to examine the utilization of other healthcare professional services, such as nurses and therapists, as these data are not systematically captured by the Saskatchewan government. We also did not have access to laboratory monitoring or MRI data, which would be important outcomes to include in future research examining the newer DMTs that require increased surveillance. We did not evaluate the effects of other factors, such as comorbidity, concurrent medication use, and adherence, which would be more appropriate for an individual-level analysis. However, in our previous work, we have shown that optimal adherence to the DMTs was 80% for the Saskatchewan MS population.[38] As is common with administrative data, we did not have access to important clinical factors that may affect hospitalization rates such as type of MS[13] and disease severity.[39] However, because we were evaluating healthcare utilization at the population level, this individual-level data was not necessary. Finally, we considered a class effect of the DMTs and therefore were not able to differentiate outcomes related to specific DMTs."*

The point 'Observational studies cannot adjust or assess all potential (unknown) confounders.' was not really discussed in the manuscript.

Thank you for identifying this. We have added a specific comment about this in the Discussion (limitations). It now reads: *"This study has limitations that should be considered. As with all*

observational studies, we were unable to identify or adjust for all potential confounders. Specific to our study, Registered First Nations and recognized Inuit people in Saskatchewan have their drug costs paid for by another government agency and were excluded from the analyses as we could not accurately determine their DMT claims…"

Authors should consider including in their introduction the current guidelines on prescribing DMTs in Canada. For eg, is this 1st or 2nd line treatment? How often is this used in comparison to other treatment options? Is this used together with other treatments?

Prescribing of the DMTs varies between provinces in Canada, although they are always used as monotherapy. During the study period, the majority of DMTs prescribed (and analyzed) were the first-line agents. We have indicated this in our Methods section where we discuss DMT use. It now reads: "*Although the first DMT (interferon-beta-1b) was approved for use in Canada in 1996, it was not available through the Saskatchewan drug plan until December 1997 (Appendix A). During the study period, the majority of DMTs prescribed were first-line agents, which include interferon-beta-1a/1b, glatiramer acetate, dimethyl fumarate, and teriflunomide (Appendix A). In Saskatchewan, prescriptions are primarily dispensed in one-month quantities, including the DMTs that were available during the study period."*

We have also modified Appendix A to differentiate between the first and second-line agents.

What happens if people died or lost to follow up during the study? How are these people considered?

Because this was a population-level study, we did not have data on the individual level. However, any individuals who died or were lost to follow-up (i.e. were no longer a beneficiary of the Saskatchewan Drug Plan) would not be included in the numerators or denominators used to determine healthcare utilization patterns. Any data prior to being lost to follow-up was included in the analyses. We have added a statement into the Methods section clarifying this. It reads: *"The association between DMT use and healthcare utilization was examined on a population-level, rather than individual-level. As such, individual-level covariates were not included in the models. Any subjects who died or were lost to follow-up (i.e. were no longer a beneficiary of the Saskatchewan Drug Plan) would not be included in the numerators or denominators used to determine healthcare utilization patterns; however, any data prior to being lost to follow-up was included in the analyses."*

In Figure 2, it was interesting that the mean length of hospital stay in the MS cohort went up and down over the rather (rather than consistently up or down). Does the authors have a possible explanation for this?

We also found the variation interesting, but do not have a definite explanation for it. Overall, we observed an in increase in the length of stay, which is consistent with other Canadian studies and trends (MS and general population). As suggested by Reviewer 1, we re-ran the trend analyses using Poisson regression, which is better suited for rates than our previously used linear regression. We still observed an increase in length of stay over time, however the trend was not statistically significant. We have revised the manuscript to reflect this change. As well, in our Discussion we comment on the increase in length of stay, and postulate that although a decrease in hospitalization rates was observed over time, it seems that individuals who are more recently hospitalized are sicker and require more complex care, resulting in longer stays.

Is it possible to separate the years on the x-axis for figures 2 and 3? It is a bit difficult to read at the moment. Perhaps put the years on an angle like it was done in figure 1?

Thank you for the suggestion – we have revised the scaling on the x-axis for all three figures.

VERSION 2 – REVIEW

REVIEWER	Raffaele Palladino Department of Public Health, Federico II University, Naples, Italy
REVIEW RETURNED	23-Oct-2019

GENERAL COMMENTS	Authors have addressed all my comments.

REVIEWER	Kate Wang Monash University, Australia
REVIEW RETURNED	30-Oct-2019

GENERAL COMMENTS	The authors have done a solid job addressing reviewer comments. Well done. I have no further suggestions.